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A SYNTHETIC ROUTE TO CARBOCYCLIC AMINONUCLEOSIDES

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The antitumor activities of 6-dimethylamino-9-(3'-amino-3'-deoxy-β-D- ribofuranosyl)-purine (puromycin aminonucleoside) and 3'-amino-3'-deoxyadenosine have generated considerable interest in the biological properties of aminonucleosides.[1] A second class of nucleoside analogs which possesses biological activity is the carbocyclic nucleosides which contain a cyclopentane ring in place of the tetrahydrofuran ring.[2,3] For reasons explained previously,[4] the hybridization of these two types of nucleosides into one molecule should provide a novel class of nucleoside analogs with potential chemotherapeutic properties. We now report a stereoselective synthesis of the "carbocyclic aminonucleoside" analogs of puromycin aminonucleoside, 3'-amino-3'-deoxyadenoside, and 3'-amino-3'-deoxyarabinosyladenine.

The recent description of an unequivocal route to 2-azabicyclo[2.2.1]hept-5-en-3-one (1)[5] offers a unique starting point for the synthesis of carbocyclic aminonucleosides of known geometric configuration. Acidic hydrolysis of 1 (2 N HCl, 25°) to cis-4-aminocyclopent-2-ene carboxylic acid hydrochloride, followed by esterification of the carboxyl function in refluxing methanol and subsequent acetylation of the amino group in acetic anhydride-pyridine, gave 2 [90% (after sublimation at 0.003 mm); mp 66-67°; m/e 183; ir (KBr) 1725, 1622, 1535 cm^{-1}; pmr ($CDCl_3$) δ 6.25 (br, NH), 5.82 (br s, CH=CH), 4.97 (m, CH-N), 3.68 (s, OCH_3), 3.64 (m, CH), 2.7-1.5 (m, CH_2) overlapping 1.91 (s, CH_3CO)]. Reduction of the methyl ester of 2 with $CaBH_4$ (THF, 25°, 18hr) gave, after acetylation, acetate 3 [89%; bp 132-134° (0.2 mm); mp 45-47°; m/e 197; ir (neat) 1735, 1638, 1530 cm^{-1}; pmr (CCl_4) δ 7.83 (br d, J=7.5 Hz, NHC=O), 5.83 (br s, CH=CH), 4.93 (m, CH-N), 4.04 (d, J=6.5 Hz, O-CH_2-CH), 3.25-2.18 (m, CH and ½CH_2), 2.07 and 1.95 (both s, $CH_3\overset{O}{\overset{\|}{C}}$-O, $CH_3\overset{O}{\overset{\|}{C}}$-N), 1.63-1.07 (m, ½$CH_2$)]. Epoxidation of 3 with m-chloroperbenzoic acid (CCl_4, reflux, 2 hr) was stereoselective due to the syn-directing allylic amide group,[6] giving only the cis-epoxide 4 [89%; mp 68-72°; m/e 213; ir (KBr) 1735, 1635, 1540, 830, 865; pmr ($CDCl_3$) δ 6.98 (br d, J=7.5 Hz, NHC=O), 4.42 (m, CH-N), 4.03 (d, J=7.0 Hz, O-CH_2-CH), 3.6-3.3 (m, $CH\overset{O}{\frown}CH$), 2.09 and 2.03 (both s, $CH_3\overset{O}{\overset{\|}{C}}$-O and $CH_3\overset{O}{\overset{\|}{C}}$-N) overlapping 2.7-0.5 (m, CH, CH_2). Removal of the acetate group (NH_3 in MeOH) gave 5. Reaction of 5 with sodium azide (aqueous methoxyethanol, buffered by NH_4Cl, 75°, 18hr) gave, after acetylation, azide 6 as the major product [83%; mp 103-104°; ir (KBr) 3255, 3090, 2110, 1745, 1645, 1555 cm^{-1}; pmr ($CDCl_3$) δ 6.38 (br d, J=8 Hz, NHC=O), 5.00 (m, CH-O), 4.8-4.2

(m, CH-NHCO), 4.12 (d, J=5.5 Hz, O-CH_2-CH), 4.60 (m, CH-N_3), 2.14, 2.12, 2.00 (all s, 3 CH_3C=O) overlapping 2.8-1.3 (m, CH, CH_2)]. A minor product, azide 11, was detected by pmr of mother liquors. Hydrogenation of azide 6 (Pt, 50 psi H_2, Ac_2O solvent) gave diacetamide 7 [70%; mp 167-168°; m/e 314; ir (KBr) 1737, 1653, 1553 cm^{-1}; pmr ($CDCl_3$) δ 7.18 (br d, J=8 Hz, NHC=O), 6.46 (br d, J=8 Hz, NHC=O), 5.3-3.9 (m, CH-O, 2 CH-N, O-CH_2), 2.11, 2.08, 2.01 (all s, 4 CH_3C=O) overlapping 2.8-1.7 (m, CH, CH_2)]. Hydrogenation of mother liquors containing a mixture of 6 and 11 gave diacetamide 12 [separated from 7 by chromatography on silica gel, 2% MeOH-$CHCl_3$; 10% from 5; mp 163.5-164.5°; m/e 314; ir (KBr) 1745, 1730 sh, 1650, 1635 sh, 1550; pmr ($CDCl_3$) δ 7.5-7.1 (m, 2 NHC=O), 5.4-5.3 (m, CH-O), 4.6-3.7 (m, 2 CH-N, O-CH_2), 2.07, 2.03, 1.98 (all s, 4 CH_3C=O) overlapped by 3.0-1.2 (m, CH, CH_2)].

The structure assignment of 7 and 12 was confirmed by acyl migration studies. When 7 was subjected to mild acidic hydrolysis (2 N HCl, 70°, 1 hr), a monoacetamide 8 was formed since acyl migration to a cis-hydroxyl facilitates hydrolysis of one acetamido group. The cis-geometry of the amino and secondary hydroxyl groups of 8 was further confirmed by conversion to the N-carbobenzyloxy derivative 9 [44%; mp 152.5-153.5°; m/e 322; ir (KBr) 1688, 1640, 1537 cm^{-1}; pmr (DMSO-d_6) δ 7.98 (br d, J=7.5 Hz, NHC=O), 7.37 (br s, C_6H_5), 6.63 (br d, J=7.5 Hz, NHC=O), 5.07 (s, O-CH_2-Ph) overlapped by 5.0-4.7 (m, OH), 4.3-3.0 (m, O-CH, 2 N-CH, O-CH_2-CH, OH), 1.68 (s, CH_3C=O) overlapped by 2.3-1.0 (m, CH_2, CH)]. Treatment of 9 with base (NaOMe in DMF, 100°, 1.5 hr), followed by acetylation, gave cyclic carbamate 10 [82%; mp 168-174° efferves.; m/e 298; ir (KBr) 1770, 1735, 1697, 1635, 1540 cm^{-1}; pmr (DMSO-d_6) δ 8.10 (br d, J=8.0 Hz, NHC=O), 5.0-3.7 (m, CH-O, 2 CH-N, CH_2-O), 2.40, 2.02, 1.88 (all s, 3 CH_3C=O) overlapped by 2.4- 1.0 (m, CH, CH_2)].

When 12 was subjected to the same acidic hydrolysis, diacetamide 13 was formed, characterized as the monomethoxytrityl derivative 14 [51% from 12; mp 158-160° efferves.; m/e 502; ir (KBr) 1650 br, 1550 br cm^{-1}; pmr ($CDCl_3$) δ 7.6-6.5 (m, 2 C_6H_5, $MeOC_6H_4$, NHC=O), 6.40 (br d, J=6.0 Hz, NHC=O), 4.43 (br s, OH), 4.2-3.5 (m, CH-O, 2 CH-N) overlapping 3.78 (s, OCH_3), 3.30 (br d, J=5.8 Hz, O-CH_2-CH), 1.95, 1.87 (both s, 2 CH_3C=O) overlapped by 2.7-1.2 (m, CH_2, CH)]. The purine moiety was formed by condensation of 8 with 5-amino-4,6-dichloropyrimidine (n-BuOH, Et_3N, reflux 18 hr) and ring closure of the resulting pyrimidine 15 (76%; mp 254-256° dec) with diethoxymethyl acetate. The resulting 6-chloropurine compound (not isolated) was reacted with NH_3, giving the carbocyclic 3'-acetamido-3'-deoxyarabinosyl-adenine analog, 16 [71%; mp 218-222° dec; m/e 306, 136, 135; uv max (0.1 N HCl)260 nm (ε 1.48 x 10^4), 258 (1.45 x 10^4); ir (KBr) 1670, 1650, 1607, 1545 cm^{-1}; pmr (DMSO-d_6) δ 8.08 (s, purine H-2 and H-8) overlapping 8.1-7.9 (br, NHC=O), 7.07 (br s, NH_2), 5.5-3.1 (m, 2-OH, CH-O, 2 CH-N, CH_2-O, H_2O), 1.89 (s, CH_3C=O) overlapped by 2.5-1.3 (m, CH, CH_2)]. Hydrolysis of 16 [$Ba(OH)_2$, reflux 6 hr] gave the carbocyclic 3'-amino-3'-deoxyarabinosyladenine, 22 [66%; mp 199-201°; ir (KBr) 1680, 1650, 1570 cm^{-1}].

The 6-amino group of 16 was blocked by reaction with N,N-dimethylformamide dimethyl acetal (DMF, 25°), giving 17 (94%; mp 227-231° dec.). The 5'-hydroxyl group was then blocked

by reaction with chloro(p-methoxyphenyl)diphenyl methane, followed by removal of the 6-N-(dimethylamino)methylene group with NH_3, giving the 5'-O-mono-p-methoxytrityl compound, 18 (75%, mp: collapses to glass at 150-154°, melts at ca. 240° dec). Treatment of 18 with methane sulfonyl chloride in pyridine (1.5 eq, 25°, 3 days), followed by hydrolysis (NaOAc, 65°, 18hr) gave the epimerized product, 19 (69%, mp: turns to glass at 160°, efferves at ca. 200°). Detritylation of 19 (97% HCOOH, 25°, 4hr) gave the 3'-acetamido carbocyclic adenosine analog, 20 [90%; m/e 306; mp 153-154°; ir (KBr) 1670, 1635, 1595, 1560 cm^{-1}; uv max (0.1 N HCl) 258 nm (ε 1.43 x 10^4), (0.1 N Na OH) 260 (1.47 x 10^4); pmr (DMSO-d_6) δ 8.13, 8.07 (both s, purine H-2 and H-8), 7.67 (br d, NHC=O), 7.10 (br s, NH_2), 6.5-3.0 (CH-O, 2CH-N, 2 OH, CH_2-O), 1.90 (s, CH_3C=O) overlapped by 2.5-1.1 (m, CH, CH_2)]. Hydrolysis of 20 [$Ba(OH)_2$, reflux, 2hr] gave the ribonucleoside analog, 21, (±)-9-[β-(3α-amino-2α-hydroxy-4β-(hydroxymethyl) cyclopentyl)]adenine [95% as acetic acid salt hemihydrate; solid foam; m/e 264; ir (KBr) 3500-3000 br, 1650, 1600, 1575 cm^{-1}; uv max (0.1 N HCl) 258 nm (ε 1.44 x 10^4), (0.1 N NaOH) 260 (1.48 x 10^4).

In an analogous series of reactions, the 6-dimethylamino analog 23 was prepared (63% from 15; mp 250-252° dec; m/e 334, 163, 164). The 5'-monomethoxytrityl derivative 24 (92%; mp 195-196°; m/e 334, 163, 164) was treated with methane sulfonyl chloride, then NaOAc, and the resulting 2'-epimer, 25 (72%, solid foam), detritylated to 26 [76%; mp 169-170°; m/e 334, 163, 164; ir (KBr) 1650, 1595, 1550; uv max (0.1 N HCl) 268 nm (ε 1.82 x 10^4), (0.1 N NaOH) 275.5 (1.85 x 10^4). Hydrolysis of 26 gave the carbocyclic analog of puromycin aminonucleoside, 27, which was converted to carbocyclic puromycin, 28, via standard methods.[4,7]

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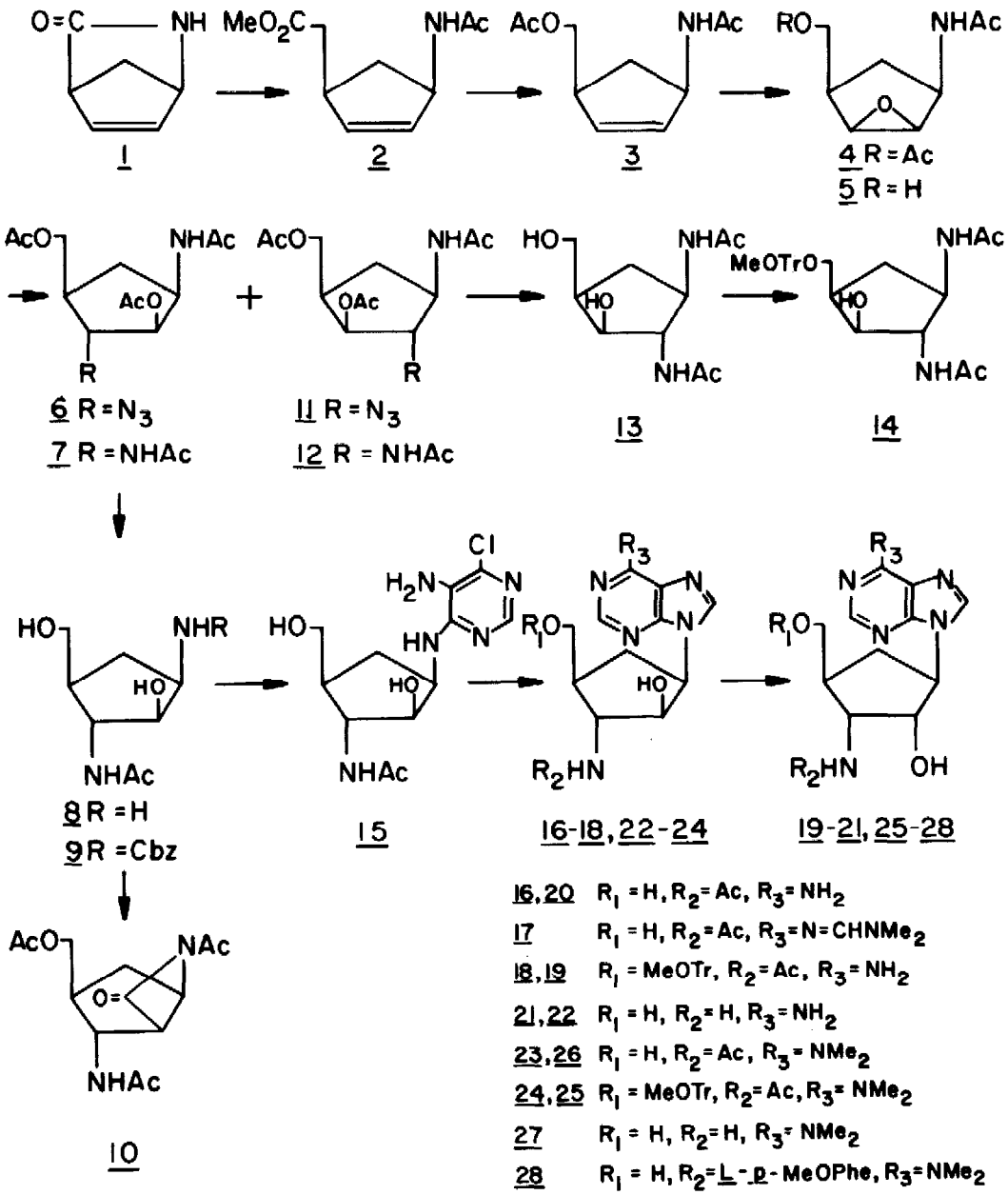
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19-21, 25-28
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27 R1=H, R2=H, R3=NMe2
28 R1=H, R2=L-p-MeOPhe, R3=NMe2